SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Coronary Stent System

Device Trade Name: Presillion™ *plus* CoCr Coronary Stent on RX System

Applicant's Name and Address: Medinol Ltd.
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Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P110004

Date of FDA Notice of Approval: April 12, 2012

Expedited: Not applicable

II. INDICATIONS FOR USE

The Presillion™ *plus* CoCr Coronary Stent on RX System s indicated for improving coronary luminal diameter in patients with symptomatic ischemic heart disease associated with stenotic lesions in de novo native coronary arteries (length ≤ 30mm) with a reference vessel diameter of 2.50 mm to 4.00 mm.

III. CONTRAINDICATIONS

The Presillion™ *plus* CoCr Coronary Stent on RX System is contraindicated for use in:

- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery system

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Presillion™ *plus* CoCr Coronary Stent on RX System labeling.

V. DEVICE DESCRIPTION

Presillion™ *plus* CoCr Coronary Stent on RX System , is a single-use device comprised of a balloon-expandable, intracoronary Presillion stent pre-mounted on a rapid-exchange delivery catheter (AccuRX™). The stent is made of L-605 Cobalt Chromium (CoCr) alloy.

The Presillion stent is cut from panels of flat sheets made of L-605 Cobalt Chromium Alloy. The sheets are laser-cut into a specified geometric pattern and then folded and welded to make a cylindrical stent. To obtain a smooth surface, the stent undergoes chemical treatment and electro-polishing.

The stent geometry is a continuous "closed cell" design, with adaptive cells capable of differential lengthening. This design enables the stent to be flexible in the unexpanded configuration, and to support the vessel, while conforming to its curvature, in the expanded configuration.

The delivery catheter for Presillion *plus* Stent System is the AccuRX balloon catheter. The AccuRX is a rapid exchange balloon catheter with shaft profiles of 1.9F (proximal) and 2.8F (distal). The AccuRX is compatible with 5F guiding catheters and 0.014" diameter guide wires. The usable length of the delivery catheter is 135cm. The Presillion *plus* Stent System specifications are listed in Table 1.

Table 1: Presillion™ *plus* Stent System Specifications

STENT INNER DIAMETER (MM)	STENT LENGTH (MM)	MINIMUM GUIDING CATHETER COMPATIBILITY	STENT NOMINAL PRESSURE (ATM)	RATED BURST PRESSURE (RBP), (ATM)	% STENT FREE AREA
2.5	8,12,17,20	5F	12	18	89.2
2.75 – 3.0	8,12,17,20,24,28,33	5F	12	18	86.9
3.5, 4.0	8,12,17,20,24,28,33	5F	12	18	86.5

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of coronary artery disease include exercise, diet and drug therapy, Percutaneous Transluminal Coronary Angioplasty (PTCA), coronary artery bypass graft (CABG) surgery, or stenting with commercially available stents. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Presillion™ *plus* CoCr Coronary Stent on RX System is marketed in Albania, Algeria, Argentina, Australia, Austria, Azerbaijan, Bahrain, Bangladesh, Belarus, Benelux, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Dominican Republic, El Salvador, Estonia, Finland, France, Ghana, Georgia, Germany, Greece, Guatemala, Honduras, Hong Kong, Hungary, Iceland, India, Indonesia, Ireland, Iran, Israel, Italy, Jamaica, Kenya, Kuwait, Latvia, Lebanon, Libya, Liechtenstein, Lithuania, Madagascar, Malta, Mauritius, Mexico, Mongolia, Morocco, Mozambique, Nepal, New Zealand, Nicaragua, Nigeria, Norway, Oman, Pakistan, Palestine, Panama, Paraguay, Poland, Portugal, Qatar, Romania, Russia, Saudi Arabia, Serbia & Montenegro, Singapore, Slovak Republic, Slovenia, South Africa, Spain, Sri Lanka, Sudan, Sweden, Switzerland, Syria, Tanzania, Thailand, Tunisia, Turkey, Trinidad and Tobago, Ukraine , United Arab Emirates, United Kingdom, Vietnam, and Yemen.

It is a CE Marked product and has been available in the European market since 2009. The Presillion *plus* Stent System has not been withdrawn from the market for any reason related to its safety or effectiveness.

As of December 31, 2011, 47, 000 Presillion *plus* Coronary Stent Systems have been distributed outside of the United States.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the Presillion™ *plus* CoCr Coronary Stent on RX System:

- Abrupt vessel closure
- Allergic reaction
- Aneurysm
- Arrhythmias
- Cardiac tamponade
- Coronary artery spasm
- Death
- Dissection
- Drug reactions to antiplatelet agents/anticoagulation agents/contrast media
- Emboli, distal (tissue, air or thrombotic emboli)
- Emergency CABG
- Failure to deliver the stent to the intended site
- Fever
- Fistulization
- Hemorrhage or hematoma
- Hypotension / Hypertension
- Infection and pain at the insertion site
- Myocardial infarction
- Myocardial ischemia

- Occlusion
- Perforation
- Prolonged angina
- Pseudoaneurysm
- Renal failure
- Repeat percutaneous intervention
- Restenosis of stented segment (greater than 50% obstruction)
- Rupture of native and bypass graft
- Stable or unstable angina
- Stent compression
- Stent misplacement / migration / embolization
- Stroke
- Thrombosis (acute, subacute or late)
- Ventricular fibrillation
- Vessel spasm

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

A1. Biocompatibility Studies

A series of GLP biocompatibility tests were conducted to demonstrate that the components of Presillion™ *plus* CoCr Coronary Stent on RX System are nontoxic. Tests were conducted on EtO-sterilized Presillion *plus* stents and AccuRX stent systems. Some biocompatibility tests were conducted on CRE-02-135 delivery system—the previous generation of the AccuRX delivery system, which did not contain the hydrophilic coating. Some biocompatibility tests were conducted by the supplier of the hydrophilic coating, as mentioned in Table 3.

All biocompatibility testing was conducted in accordance with one or more of the following general regulations and guidance documents:

- Guidance for Industry and FDA Staff "Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems", April 18, 2010
- USP <151> PYROGEN TEST
- Good Laboratory Practices Regulations (21 CFR § 58)
- ISO 10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing

Table 2: Biocompatibility Testing Conducted on the Presillion *plus* Stent

BIOLOGICAL EFFECT	TEST NAME	TEST RESULTS	
		PASS/FAIL	EFFECT
Cytotoxicity	Cytotoxicity Study Using the ISO Elution Method-1X Minimal Essential Media Extract	Pass	Non-Cytotoxic
Sensitization	ISO Maximization Sensitization (Extract - 0.9% Sodium Chloride Solution)	Pass	Non-Sensitizing
Sensitization	ISO Maximization Sensitization (Extract - Sesame Oil, NF)	Pass	Non-Sensitizing
Intracutaneous Reactivity (Irritation)	ISO Intracutaneous Study - Extract - 0.9% Sodium Chloride Solution	Pass	Non-Irritating
Intracutaneous Reactivity (Irritation)	ISO Intracutaneous Study - Extract - Sesame Oil, NF	Pass	Non-Irritating
Systemic toxicity (acute)	USP and ISO Systemic Toxicity Study - Extract-0.9% Sodium Chloride Solution	Pass	Non-Toxic
Systemic toxicity (acute)	USP and ISO Systemic Toxicity Study - Extract- Sesame Oil, NF	Pass	Non-Toxic
Subchronic Toxicity	Rat Subchronic Intravenous Toxicity Study-0.9% Sodium Chloride Solution Extract	Pass	Non-Toxic
Genotoxicity	Genotoxicity, Bacterial Reverse Mutation Study -0.9% Sodium Chloride Solution Extract	Pass	Non-Mutagenic
Genotoxicity	Genotoxicity, Bacterial Reverse Mutation Study -Dimethyl Sulfoxide (DMSO) Extract	Pass	Non-Mutagenic
Pyrogenicity	Pyrogen Study - Material Mediated- 0.9% Sodium Chloride Solution Extract	Pass	Non-Pyrogenic
Implantation	ISO Muscle Implantation Study - 4 week ISO Muscle Implantation Study - 2 Week	Pass	Non-Irritant; No Tissue Response
Hemolysis (Extraction)	In Vitro Hemolysis Study (Modified ASTM Method)-0.9% Sodium Chloride Solution Extract	Pass	Non-Hemolytic
Hemolysis (Direct Contact)	In Vitro Hemolysis Study (Modified ASTM Direct Contact)	Pass	Non-Hemolytic
Hemolysis	In Vitro Hemolysis Study (ASTM 756-00)	Pass	Non-Hemolytic
Complement Activation	C3a assay	Pass	Non- complement activator
Complement Activation	SC5b9 assay	Pass	Non complement activator

Table 3: Biocompatibility Testing Conducted on Presillion *plus* Delivery System

BIOLOGICAL EFFECT	TEST NAME	TEST RESULTS	
		PASS/FAIL	EFFECT
Cytotoxicity	Cytotoxicity Study Using the ISO Elution Method-1X Minimal Essential Media Extract	Pass	Non-Cytotoxic
Sensitization	ISO Maximization Sensitization Extract - 0.9% Sodium Chloride Solution	Pass	Non-Sensitizing
	ISO Maximization Sensitization Extract - Sesame Oil, NF	Pass	Non-Sensitizing
Intracutaneous Reactivity (Irritation)	ISO Intracutaneous Study – Extract - 0.9% Sodium Chloride Solution Extract	Pass	Non-Irritating
	ISO Intracutaneous Study – Extract - Sesame Oil, NF Extract	Pass	Non-Irritating
Systemic toxicity */**(acute)	USP and ISO Systemic Toxicity Study – Extract - 0.9% Sodium Chloride Solution Extract	Pass	Non-Toxic
	USP and ISO Systemic Toxicity Study – Extract - Sesame Oil, NF Extract	Pass	Non-Toxic
Pyrogenicity**	Pyrogen Study - Material Mediated - 0.9% Sodium Chloride Solution Extract	Pass	Non-Pyrogenic
Hematology *(Direct Contact)	In Vitro Hemolysis Study (Modified ASTM Direct Contact)	Pass	Non-Hemolytic
Hemolysis	ASTM Hemolysis Study CMF -PBS Extract	Pass	Non-Hemolytic
Complement Activation	C3a assay	Pass	Low potential activator of the complement system
Complement Activation	SC5b9 assay	Pass	Non-activating

* Tests were conducted on CRE-02-135 delivery systems.
** Tests were conducted and provided by the supplier of the Hydrophilic coating.

Based on the above results for testing conducted on the Presillion *plus* Stent System (AccuRX), the previous generation delivery system, and the hydrophilic coating, the Presillion *plus* Stent System has been demonstrated to be non-toxic and appropriately biocompatible for clinical use.

A2. *In-Vitro* Engineering Testing

In-vitro engineering testing was conducted on Presillion *plus* Stent System in accordance with the U.S. FDA's April 18, 2010 guidance "Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems."

This testing is summarized in Table 4. A "Pass" result denotes that the test results met product specifications and/or the recommendations in the above referenced guidance document.

The relevant tests outlined in the guidance were conducted to demonstrate the safety and effectiveness of the Presillion *plus* Stent System.

Table 4: Summary of in-vitro bench testing

TEST	TEST DESCRIPTION	RESULTS
Material Characterization Testing		
Material Analysis	The Presillion *plus* Stent is manufactured from sheets of L-605 cobalt chromium alloy. The sheet was analyzed for chemical composition and mechanical properties and was shown to conform to ASTM Standard F-90 for chemical analysis and inclusion/ impurity content.	**Pass**
Corrosion Testing	The Presillion™ *plus* stent was tested according to ASTM F2129-01 "Standard Test Method for Conducting Cyclic Potentiodynamic Measurements to Determine the Corrosion Susceptibility of Small Implant Devices" to demonstrate that the finished stents exhibit acceptable corrosion resistance. The Presillion™ *plus* stent demonstrated no pitting/fretting or crevice corrosion after completing 400 million cycles (10 years) of accelerated pulsatile fatigue, in an overlapped, bent configuration.	**Pass**
Stent Dimensional and Functional Attribute		
Stent Dimensional Verification	Measurements were taken of the Presillion *plus* stent strut width and thickness. All stents met product specifications.	**Pass**
Stent Free Area (Metal to Artery Ratio)	The stent free area is complementary to the metal to artery ratio, which is the ratio between the stent's outer surface and the area of the vessel. The calculated Percent Free Area is 89.2% for the 2.5mm diameter, 86.9% for the 2.75-3.0mm diameter, and 86.5% for the 3.5-4.0mm diameter stents.	**Pass**
Foreshortening / Elongation & Non-Uniformity	The foreshortening test determined the change in length of the Presillion *plus* stent between the catheter-mounted condition and the condition in which the stent was expanded (deployed) condition to the nominal diameter and to RBP. Stent length was measured prior to and after expansion to calculate length change.	**Pass**
Recoil	The system was inflated to nominal and maximum labeled diameters and measured for stent diameter at three locations along the stent length, for both 0deg and 90deg orientations. The system was then deflated and the same measurements were repeated. The percent recoil is calculated by subtracting the average stent inner diameter (ID) after recoil from the average stent ID before recoil,	**Pass**

TEST	TEST DESCRIPTION	RESULTS
	divided by the average stent ID before recoil and then multiplying by 100. All stents met product specifications.	
Stent Integrity	Testing was conducted to ensure that the visual and handling performance of the Presillion™ *plus* Stent System conforms to the specification. Acceptable stent integrity was defined as no broken struts, missing struts, cracked struts or mechanical damage. The test results for visual and handling performance were acceptable.	**Pass**
Radial Stiffness and Radial Strength	Testing was conducted to determine the radial strength of the stent under compression force. Stents were expanded to RBP diameters, placed in an IRIS tester, and subjected to incrementally increasing compression. The radial stiffness and radial strength were recorded. All stents met product specifications.	**Pass**
Mechanical Properties: Tensile Strength and Elongation	Mechanical properties of the stent raw material (L605) were evaluated. Mechanical properties of stent raw material were compared with mechanical properties of stent raw material that was subjected to all relevant stent manufacturing processes. Results of the tensile strength, elongation, and yield tests met material specifications.	**Pass**
Stress/Strain Analysis (FEA)	**This analysis was conducted to determine the state of stress analysis of the Presillion™ *plus* stent from the manufacturing process through clinical conditions of deployment to maximum labeled diameter, overlap, and pulsatile fatigue in a 15mm static bend.** Acceptance criteria: maximum stresses shall not exceed material UTS as well as a safety factor of NLT 1 for calculation of radial fatigue in an overlapped, bent configuration. The acceptance criteria were met.	**Pass**
Fatigue Analysis	**This analysis was conducted to determine the state of fatigue analysis of the Presillion™ *plus* stent from the manufacturing process through clinical conditions of deployment to maximum labeled diameter, overlap, and pulsatile fatigue in a 15mm static bend.** The Goodman analysis fatigue safety factors demonstrated that failures due to fatigue alone will not likely occur.	**Pass**
Accelerated Durability Testing (radial fatigue)	**Testing was conducted to determine whether the Presillion™ *plus* stent can adequately withstand accelerated durability conditions while the stents are bent (radius of 15mm) and overlapped and to determine that the stent can adequately withstand expected *in vivo* cyclic loading conditions.** Acceptance criteria: No durability failure (cracks, breaks) detected after subjected to 400 million cycles of accelerated durability testing. Following cycling, stents were visually inspected under 40X magnification. In addition, SEM pictures were taken of stent surfaces. No signs of strut cracking or breaking were detected, and all stents passed.	**Pass**

TEST	TEST DESCRIPTION	RESULTS
Accelerated Durability Testing (dynamic loading)	Testing was conducted to determine that the Presillion™ *plus* stent can adequately withstand accelerated durability conditions while the stents are bent (radius of 15mm was chosen) and overlapped, and subjected to dynamic fatigue loading. The Presillion™ *plus* stent met acceptance criteria.	**Pass**
Magnetic Resonance Imaging (MRI)	Non-clinical testing has demonstrated the Presillion Stent, in single and overlapped configurations up to 73mm of length, is MR Conditional. It can be scanned safely, immediately after placement, under the following conditions: • Static magnetic field of 1.5 or 3 Tesla • Maximum spatial gradient magnetic field of 1100 Gauss/cm or less • Maximum whole body averaged specific absorption rate (SAR) of 2.0 W/kg or less with the MR system operating in the Normal Operating Mode for 15 minutes of scanning (per pulse sequence) ***Additional MRI Heating Information*** Stent heating was derived by using the measured non-clinical, in vitro temperature rises in a GE Excite 3 Tesla scanner and in a Siemens Magnetom 1.5 Tesla coil in combination with the whole body averaged specific absorption rates (SARs) in the ASTM phantom. At overlapped lengths of up to 73mm, the Presillion stent produced a nonclinical maximum local temperature rise of 2.5°C scaled to a maximum whole body averaged SAR of 2.0 W/kg (normal operating mode) for one sequence of 15 minutes. These calculations do not take into consideration the cooling effects of blood flow. ***Image Artifact Information*** The calculated image artifact extends approximately 4.7mm from the perimeter of the device diameter and 1mm beyond each end of the length of the stent when scanned in non-clinical testing using a Spin Echo sequence. With a Gradient Echo sequence, the calculated image artifact extends 7.4mm beyond the perimeter of the diameter and 3mm beyond each end of the length, with both sequences partially shielding the lumen; measurements performed in a 3.0 Tesla Magnetom Trio, Siemens Medical Solutions, software version Numaris/4, syngo MR 2004A 4VA25A, actively shielded MR system.	**Pass**
Radiopacity	This evaluation was performed to confirm that the Presillion *plus* stent is adequately visible with	**Pass**

TEST	TEST DESCRIPTION	RESULTS
	fluoroscopic imaging equipment. When compared to comparable sizes of the approved NIRFLEX™ stent, the Presillion *plus*™ stent demonstrated equivalent visibility under fluoroscopy.	
Conformability	This testing was intended to measure the flexibility of a deployed Presillion™ *plus* stent. Stents were subjected to a 2 mm deflection in 2-point bending and the resistive force was recorded. The Presillion™ *plus* (Presillion™ *plus*) stent demonstrated a lower force when compared to the approved NIRFLEX stent, for all sizes except 3.5mm. Forces for the 3.5mm stent were higher compared to the NIRFLEX but lower force compared to other US approved stents (NIR stent and BX Sonic - Velocity) .	**Pass**
Over Expansion	The Over Expansion test demonstrates that the Presillion™ *plus* stent can be expanded above the nominal diameter without failure, as per product specifications. The catheter was inflated to RBP and then was replaced with other catheters of larger diameter to achieve over-expansion of the stent. The stent was examined in an over-expanded state under microscope, at 20X or more, for broken struts or cracks. No broken struts or cracks were observed in any samples.	**Pass**
Delivery System Dimensional and Functional Attributes		
Dimensional Verification	Measurements were taken to verify that the general catheter dimensions match specifications.	**Pass**
Delivery, Deployment and Retraction	Design verification testing demonstrated that Presillion *plus* Stent System meets specifications and user requirements for delivery, deployment, and retraction.	**Pass**
Crossing Profile	This testing determined the crimped stent outer diameter. Measurements were taken at various locations along the length of the stent and averaged to calculate the mean outer diameter. All samples met product specifications.	**Pass**
Retraction Force & Catheter Withdrawal Time	This testing was conducted to verify that the system is compatible with the specified guiding catheter and can be safely withdrawn into the guiding catheter after inflation/deflation, and to measure the force required to retract the catheter into the guiding catheter after deflation and the catheter withdrawal time. All systems met product specifications.	**Pass**
Balloon Rated Burst Pressure	This testing demonstrated that the Presillion *plus* systems can be inflated in unconstrained condition and will not rupture below the rated burst pressure (RBP) at 99.9% reliability, and will not rupture below the maximum labeled compliance (MLC) pressure at 99% reliability. All systems met product specifications and confidence/ reliability limits.	**Pass**
Balloon Fatigue	In this testing, repeated inflation/deflation cycles were	**Pass**

TEST	TEST DESCRIPTION	RESULTS
	performed, demonstrating Presillion™ *plus* Stent System can sustain NLT 10 repeated inflations to the rated burst pressure inside the stent without bursting. All samples withstood a minimum ten (10) repeated inflations to rated burst pressure with 90% reliability and 95% confidence.	
Balloon Compliance	This testing determined how the diameter of a deployed balloon varies with applied balloon pressures. All systems met product specifications.	**Pass**
Balloon Inflation & Deflation Time	This testing determined the amount of time required to inflate or deflate the delivery catheter balloon. All systems met product specifications for deflation times.	**Pass**
Catheter Bond Strength	This testing was conducted to measure the force at break for all catheter junctions: body bond, RE-port and proximal fuse bonds. All systems met product specifications.	**Pass**
Flexibility & Kink Test	This test determined the minimum radius of curvature that the system can accommodate without kinking. All systems met product specifications.	**Pass**
Particulate Evaluation and Coating integrity	This test evaluated the particulate matter shed by the stent system during navigation of challenging vasculature followed by deployment and retraction. The Presillion *plus* Stent System was tracked through a simulated tortuous artery model and deployed to RBP inside a simulated vasculature. The stent system was then retracted into the guiding catheter. Water was drawn through the vasculature, and the particle quantities and sizes were counted and recorded. All stents met product specifications. After retraction, the coating integrity was examined and subjected to a visual inspection which quantified the size and number of coating defects. The Presillion *plus* Stent System demonstrated acceptable coating integrity following simulated use.	**Pass**
Stent Securement (Distal mode)	This test determined the amount of force required to displace the stent a critical distance from its original, crimped position on the delivery system, simulating dislodgment during retraction into the guiding catheter. The test was performed after a pre-conditioning tracking through a tortuous artery model. All systems met product specifications.	**Pass**
Stent Securement (Proximal mode)	This test determines the amount of force required to displace the stent a critical distance from its original, crimped position on the delivery system, simulating dislodgment during tracking though a lesion. The test was performed after a pre-conditioning tracking through a tortuous artery model. All systems met product specifications.	**Pass**

A3. Package Integrity Testing

The packaging validation testing was conducted through an accelerated aging process reflecting 2 years of shelf life. The packaging configuration for Presillion *plus* Stent System meets all current specifications. The Presillion *plus* sterility pouch exhibits acceptable integrity and maintains this functional ability throughout the current product shelf life of up to two years.

A4. Shelf-Life (Aging) Testing

Samples of Presillion *plus* Stent System were subjected to accelerated aging and evaluated through functional testing to ensure adherence to the product specifications. The data collected to date ensures a product shelf life of two (2) years for Presillion *plus* Stent System.

A5. Sterilization

The Presillion™ *plus* CoCr Coronary Stent on RX System is sterilized using ethylene oxide (EO) sterilization. The sterilization cycle, conducted at 45°C and using a 90% ethylene oxide and 10% CO_2 mixture, has been validated according to ISO 11135-1 "Sterilization of health care products - Ethylene oxide - P.1: Requirements for development, validation and routine control of a sterilization process for medical devices." The results obtained from the sterilization validation studies show that the sterilization process provides a Sterility Assurance Level (SAL) of 10^{-6}. The Presillion *plus* Stent Systems were tested successfully for EO residuals and met the limits specified in ISO 10993-7. In addition, the amount of bacterial endotoxins was verified to be within specification limits using the LAL test, and routine testing is conducted for every sterilization lot.

B. Animal Studies

The Presillion™ *plus* CoCr Coronary Stent on RX System was evaluated in six (6) GLP animal studies at CBSET Inc, Lexington, MA.

Three of the studies (UW S00002, UWS00003, and UWS00004) were conducted to assess the acute performance, safety, and effectiveness of the Presillion *plus* at different time points: 28 days, 90 days, and 180 days.

Except for differences in injury scores, there were no statistical differences in the histomorphometric analysis between the Presillion™ *plus* and the NIRFLEX™ (US-approved product) stent groups at 28, 90 and 180 days. Injury scores were low in both groups, and the differences were not considered biologically relevant. Overall, the responses recorded for both stents were comparable at 28, 90, and 180 days.

Two studies (UWS00005 and UWS00007) evaluated the performance characteristics of the Presillion *plus* Stent on Sonic delivery system at acute (0) and five (5) days post-implant, respectively. The results from these studies show no adverse effect, acutely or at five (5) days, as well as non-inferiority when the test device was compared to the control.

Characteristics such as deliverability and acute performance were semi-quantitatively rated mostly as "excellent" or "good" by the study interventionalists.

One study (UWS00008) was conducted to evaluate the acute (day 0) performance characteristics (such as deployment at nominal pressure, deflation time, insertion and withdrawal through an implanted stent, and deliverability through a tortuous vessel) of Presillion™ *plus* Catheter System compared to the Presillion stent system. The acute performance of the Presillion™ *plus* Catheter System was found to be acceptable.

Summaries of the major animal studies performed to support product safety are included in Table 5.

Table 5: Summary of Animal Studies

Study #	Study Design	Animal Model	# of Stents	Follow up duration	Endpoints
UWS00002	Test article: Presillion *plus* (3.00x16 mm) Control: NIRFLEX (3.00×16 mm)	Yucatan Swine (5) (RCA; LAD; LCX) 1 stent/vessel 2-3 stents/animal	Test: 8 Control: 8	28 days	Assess the acute performance, safety and efficacy of Presillion™ *plus* stent at 28 days
UWS00003	Test article: Presillion *plus* (3.00x16 mm) Control: NIRFLEX (3.00×16 mm)	Yucatan Swine (5) (RCA; LAD; LCX) 1 stent/vessel 2-3 stents/animal	Test:8 Control:7	90 days	Assess the acute performance, safety and efficacy of Presillion™ *plus* stent at 90 days
UWS00004	**Test article:** Presillion *plus* (3.00x16 mm) **Control**: NIRFLEX (3.00×16 mm)	Yucatan Swine (5) (RCA; LAD; LCX) 1 stent/vessel 2-3 stents/animal	Test: 8 Control: 6	180 days	Assess the acute performance, safety and efficacy of Presillion™ *plus* stent at 180 days
UWS00005	**Test article:** Presillion *plus* (2.75x33 mm) Presillion *plus* (4.00x33 mm) **Control:** NIRFLEX (2.75×32 mm) NIRFLEX (4.00×32 mm)	Yucatan Swine (2) (RCA; LAD; LCX; PDA) 1-2 stents/vessel 4-7 stents/animal	Test: 2.75mm=2, 4.00mm=3 Control: 6 2.75mm=3, 4.00mm=3	Acute	Evaluate the acute performance characteristics: • Long systems to evaluate deliverability to distal targets across tortuous anatomy • Highest diameter to test the worst case of inflation/deflation time and withdrawal profile and challenge

Study #	Study Design	Animal Model	# of Stents	Follow up duration	Endpoints
UWS00007	**Test article:** Presillion (3.00x17 mm) **Control:** NIRFLEX (3.00×16 mm)	Yucatan Swine (6) (RCA; LAD; LCX) 1 stent/vessel 2-3 stents/animal	Test:8 Control:8	5 days	Assess the safety and efficacy
UWS00008	**Test article:** Presillion *plus* (3.00x17 mm) **Control:** Presillion (3.00x17 mm)	Yucatan Swine (4) (RCA; LAD; LCX) 2 stents/vessel 6 stents/animal	Test: 12 Control:12	Acute	Evaluate the acute performance characteristics by the following comparisons: • Delivery through tortuous vessel and through an already deployed stent in a curve • Deployment at nominal and at rated burst pressure • Deflation time • Withdrawal of deflated balloon catheter • Insertion and withdrawal of undeployed stent system through implanted stent

X. SUMMARY OF PRIMARY CLINICAL STUDIES

A. PIONIR

The PIONIR™ clinical study was the pivotal study conducted to demonstrate the safety and effectiveness of the Presillion™ *plus* CoCr Coronary Stent on RX System . As the Presillion™ *plus* CoCr Coronary Stent on RX System represents minor modifications to the Presillion™ Stent System (the stent is identical in both systems), two additional clinical studies are applicable and considered supportive studies of the Presillion™ *plus* CoCr Coronary Stent on RX System:

- The control arm from the BLAST study – a phase II, randomized, double blind clinical study of the Presillion Stent System in combination with Liposomal Alendronate, compared to the Presillion Stent System alone, in treatment of de novo stenotic lesions in native coronary arteries in a population undergoing PCI.
- The Belgian Registry – a single arm registry, evaluating the safety of Presillion Stent System in the treatment of de novo stenotic lesions in native coronary arteries.

A.1 Study Design

The PIONIR is a non-randomized, multi-center, prospective, single arm clinical study conducted in Germany, Sweden, Belgium and Israel.

The main objective of this study was to collect and analyze additional information about the safety and effectiveness of Presillion™ Stent System or Presillion™ *plus* CoCr Coronary Stent on RX System in the treatment of single de novo stenotic lesions in native coronary arteries with length ≤ 30mm and a reference vessel diameter of 2.50mm to 4.00mm. The intention was to cover the index lesion with one stent of adequate length. For bailout procedures or in the event of a sub-optimal result, further stenting was employed, at investigator's discretion, using the Presillion™/Presillion™ *plus* Stent Systems, as required. Given the similarities between the Presillion and Presillion *plus* Stent Systems, either could be used in this study.

The primary endpoint is the incidence of target vessel failure (TVF): cardiac death, target vessel myocardial infarction (MI [Q wave or non-Q wave]), or clinically driven target vessel revascularization (TVR) by percutaneous or surgical methods, within 270 days of treatment with the Presillion™/Presillion™ *plus* Stent System. This rate is compared with a performance goal derived using a meta-analysis of literature articles reporting outcomes with approved bare metal coronary stents.

The clinical trial design for PIONIR is summarized in Table 6.

Table 6: PIONIR Clinical Trial Design

	PIONIR
Study Type/Design	• Multi-center study (n=16), performed in Europe (Germany, Sweden and Belgium) and Israel • Prospective • Single arm • Patients treated with Presillion™ or Presillion™ plus CoCr Coronary Stent on RX System, as available
Number of Patients	Total 278
Lesion Criteria	Single de novo stenotic lesions in native coronary arteries (length ≤ 30 mm) with a reference vessel diameter of 2.50 mm to 4.00 mm
Stent sizes (mm)	• Diameter 2.5; Lengths: 8, 12, 17, 20 • Diameters: 2.75, 3.0, 3,5, 4.0; Lengths 8, 12, 17, 20, 24, 33
Anti-Platelet Therapy	• Aspirin, indefinitely • Clopidogrel, Prasugrel, or Ticlopidine, for a minimum of 1 month post procedure
Primary Endpoint	Target Vessel Failure (TVF) defined as cardiac death, target vessel myocardial infarction (MI [Q wave or non-Q wave]), or clinically driven target vessel revascularization (TVR) by percutaneous or surgical methods at 270 days
Follow-Up	At: discharge, 30 days, 180 days, 270 days, and 1 year
Sponsor	Medinol Ltd.

A.2 Clinical Inclusion/Exclusion Criteria

Enrollment in the PIONIR clinical trial was limited to subjects who met the eligibility criteria and who provided a signed informed consent form prior to enrollment.

General Inclusion Criteria

1. Patient ≥ 18 years old.
2. Eligible for percutaneous coronary intervention (PCI).
3. Patient understands the nature of the procedure and provides written informed consent prior to the catheterization procedure.
4. Patient is willing to comply with specified follow-up evaluation and can be contacted by telephone.
5. Acceptable candidate for coronary artery bypass graft (CABG) surgery.
6. Stable angina pectoris (Canadian Cardiovascular Society (CCS) 1, 2, 3 or 4) or unstable angina pectoris (Braunwald Class 1-3, B-C) or a positive functional ischemia study (e.g., ETT, SPECT, Stress echocardiography or Cardiac CT).
7. Male or non-pregnant female patient (Note: females of child bearing potential must produce a negative pregnancy test result prior to enrollment in the study).

Angiographic Inclusion Criteria

1. Patient indicated for elective stenting of a single stenotic lesion in a native coronary artery.
2. Reference vessel ≥ 2.5mm and ≤ 4.0mm in diameter by visual estimate.
3. Target lesion ≤ 30mm in length by visual estimate (intention should be to cover the whole lesion with one stent of adequate length).
4. Target lesion stenosis ≥ 50% and < 100% by visual estimate.

Exclusion Criteria:

General Exclusion Criteria

1. Currently enrolled in another investigational device or drug trial that has not completed the primary endpoint or that clinically interferes with the current study endpoints.
2. Previously enrolled in another stent trial in the previous 2 years.
3. Any planned elective surgery or percutaneous intervention within subsequent 9 months.
4. A previous coronary interventional procedure of any kind within the 30 days prior to the procedure.
5. The subject requires staged procedure of either the target or any non-target vessel within 9 months post-procedure.
6. The target lesion requires treatment with a device other than PTCA prior to stent placement (such as, but not limited to, directional coronary atherectomy, excimer laser, rotational atherectomy, etc.).
7. Previous drug eluting stent (DES) deployment anywhere in the target vessel.
8. Any DES deployment anywhere within the past 12 months.
9. Any previous stent placement within target lesion segment within 15 mm (proximal or distal) of the target lesion.

10. Co-morbid condition(s) that could limit the patient's ability to participate in the trial or to comply with follow-up requirements, or impact the scientific integrity of the trial.
11. Concurrent medical condition with a life expectancy of less than 12 months.
12. Documented left ventricular ejection fraction (LVEF) < 25% at the most recent evaluation.
13. Evidence of an acute myocardial infarction (MI) within 72 hours of the intended trial procedure.
14. History of cerebrovascular accident or transient ischemic attack in the last 6 months.
15. Leukopenia (leukocytes <3.5 × 109 / liter).
16. Neutropenia (Absolute Neutrophil Count < 1000/mm3) ≤ 3 days prior to enrollment.
17. Thrombocytopenia (platelets < 100,000/mm3) pre-procedure.
18. Active peptic ulcer or active GI bleeding.
19. History of bleeding diathesis or coagulopathy or inability to accept blood transfusions.
20. Known hypersensitivity or contraindication to aspirin, heparin or bivalirudin, clopidogrel, prasugrel or ticlopidine, cobalt, nickel, L-605 Cobalt chromium alloy or sensitivity to contrast media, which cannot be adequately pre-medicated.
21. Serum creatinine level >2.5 mg/dl within 7 days prior to index procedure.
22. Subject is currently or has been previously enrolled in the PIONIR study.

Angiographic Exclusion Criteria

1. Unprotected left main coronary artery disease (obstruction greater than 50% in the left main coronary artery that is not protected by at least one non-obstructed bypass graft to the LAD or Circumflex artery or a branch thereof).
2. Target vessel exhibiting multiple lesions with greater than 60% diameter stenosis outside of a range of 5mm proximal and distal to the target lesion based on visual estimate or on-line QCA.
3. Target lesion exhibiting an intraluminal thrombus (occupying > 50% of the true lumen diameter) at any time.
4. Lesion location that is aorto-ostial or within 5mm of the origin of the left anterior descending (LAD) or left circumflex (LCX).
5. Target lesion with side branches > 2.0mm in diameter.
6. Target lesion involving a bifurcation (either stenosis of both main vessel and major branch or stenosis of just major branch).
7. Target lesion with severe calcification.
8. Target vessel exhibiting excessive tortuosity that may impede stent delivery and deployment at target lesion.
9. Target lesion that is located in a native vessel distal to an anastomosis with a saphenous vein graft or a left/right internal mammary artery (LIMA/RIMA) bypass.

A.3 Follow-up Schedule

All subjects were followed up to 1 year. All subjects were required to have a hospital or office follow-up visit at 30 days, 6 months, 9 months and 1 year.

A.4 Clinical Endpoints

The PIONIR clinical trial primary endpoint was TVF at 9 months, defined as the composite of:

1. Cardiac death
2. Target Vessel Myocardial Infarction (MI [Q wave or non-Q wave])
3. Clinically-indicated Target Vessel Revascularization (TVR).

TVF at 9 months was compared to a performance goal.

Other key secondary clinical endpoints included the following:

1. All Death at 30, 180, 270, and 360 days
2. Cardiac Death at 30, 180, 270, and 360 days
3. MI at 30, 180 and 270, and 360 days
4. Clinically driven target lesion revascularization (TLR) at 30, 180, 270, and 360 days
5. TVR at 30, 180, 270 and 360 days
6. Acute Success Rates
   - Device Success: Attainment of < 50% final residual stenosis of the target lesion using only Presillion™ or Presillion™ *plus* Stent Systems
   - Lesion Success: Attainment of < 50% final residual stenosis of the target lesion using any percutaneous method
   - Procedure Success: Attainment of < 50% residual stenosis of the target lesion and no in-hospital death, MI, or TLR
7. Bleeding or Vascular Complications at hospital discharge
8. Stent Thrombosis at hospital discharge, 30, 180, 270, and 360 days

A.5 Accountability of PMA Cohort

At the time of database lock for the 9 month primary endpoint, of 278 ITT subjects enrolled, 94.2% (262) subjects were available for analysis. At 12 month – study completion, 96.7% (269) ITT subjects were available.

Table 7: Patient Accountability

Patient Group	**# of patients at 9 Month**	**# of patients at 12 Month**
Intent-to-Treat	278	278
Per-Protocol	244	250
Patients that did not meet Inclusion/Exclusion Criterion	20	20
Patients that did not receive an implanted Study Stent at target lesion	5	5
Patients that withdrew consent	2	2
Reason Exit from the study	7	9
Subject withdrew consent	2	2
Death	4	4
Lost to follow-up	1	3

A.6 Study Population Demographics and Baseline Parameters

Table 8 describes the characteristics and baseline parameters of patients in the PIONIR Study:

Table 8: Patient Characteristics

CHARACTERISTIC	% OF NUMBER OF PATIENTS (278)
Age (years)	65.5±10.6
Male	76.3%
Current smokers	23.7%
Hypercholesterolemia	76.2%
Hypertension	72.3 %
Previous MI	27.8%
Diabetes • Diet controlled • Oral Hypoglycemics • Insulin	20.5% 4.0% 12.2% 4.3%

A.7. Safety and Effectiveness Results

Principal safety and effectiveness results are shown in Table 9.

- The 270-day TVF rate was 8.7% and the upper bound of the exact one-sided 95% confidence interval was 12.7%. Since this upper bound is less than the established performance goal of 16.46%, the performance goal is considered to have been met.
- The 270-day TLF rate was 7.6% (21/276). Lesion success was achieved in 100.0% (281/281) of cases. Device success was achieved in 98.2% (276/281) of cases and Procedural success was achieved in 97.8% (272/278) of cases.

Table 9: Safety and Effectiveness Results through 270 days

	PRESILLION™ /PRESILLION™ *PLUS* (N=278 PATIENTS N=281 LESIONS)	[95% CI]
PRIMARY ENDPOINT		
TVF-Free at 270 Days	91.3%	[88.0%,94.6%]
EFFECTIVENESS MEASURES		
Lesion Success	100.0% (281/281)	[98.7%,100.0%]
Device Success	98.2% (276/281)	[95.9%,99.4%]
Procedure Success	97.8% (272/278)	[95.4%,99.2%]
TVF-Free at 30 Days	97.5%	[95.6%,99.3%]
Target Vessel MI-Free at 30 Days	97.5%	[95.6%,99.3%]
Clinically Driven TLR-Free at 30 Days	98.9%	[97.7%,100.0%]
Clinically Driven TVR-Free at 30 Days	98.9%	[97.7%,100.0%]
Death-Free at 270 Days	98.6%	[97.1%,100.0%]
Target Vessel MI-Free at 270 Days	96.8%	[94.6%,98.9%]
Clinically Driven TLR-Free at 270 Days	94.9%	[92.3%,97.5%]
Clinically Driven TVR-Free at 270 Days	93.5%	[90.5%,96.4%]
SAFETY MEASURES **Principal Adverse Events through 270 days**		
TVF to 30 Days	2.5% (7/277)	[1.0%,5.1%]
All Death to 30 Days	0.4% (1/277)	[0.0%,2.0%]
Target Vessel MI to 30 Days	2.5% (7/277)	[1.0%,5.1%]
TVF to 270 Days	8.7% (24/276)	[5.7%,12.7%]
TLF to 270 Days	7.6% (21/276)	[4.8%, 11.4%]
All Death to 270 Days	1.4% (4/276)	[0.4%,3.7%]
Target Vessel MI to 270 Days	3.3% (9/276)	[1.5%,6.1%]
Stent Thrombosis at Discharge	0.7 (2/278)	[0.1%, 2.6%]
Stent Thrombosis to 270 Days (ARC Definite /Probable)[1] • Acute (0-1 days) • Sub acute (2-30 days)	1.1% (3/276) 0.4% (1/278) 0.7% (2/277)	[0.2%,3.1%]
Bleeding Complications at Discharge	0.0% (0/278)	[0.0%,1.3%]
Vascular Complications at Discharge	1.4% (4/278)	[0.4%,3.6%]

Target Vessel Failure – Cardiac death, target vessel myocardial infarction (Q Wave and non-Q-wave), or clinically driven target vessel revascularization (TVR) by percutaneous or surgical methods.
Target Vessel Revascularization – Any percutaneous intervention of surgical bypass of any segment of the target vessel.
Target Lesion Revascularization – Any percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion.
Stent Thrombosis – Thrombus or closure within the stented vessel. Acute (0 – 24 hours post stent implantation), Subacute (>24 hours – 30 days post stent implantation), or late (30 days – 1 year post stent implantation).
Bleeding complication – A procedure-related hemorrhagic event that requires a transfusion and/or surgical intervention
Vascular complication – May include the following: Pseudoaneurysm, Arteriovenous fistula (AVF), Peripheral ischemia/nerve injury, Vascular event requiring transfusion or surgical repair.
Lesion success - the attainment of <50% final residual stenosis of the target lesion using only Presillion or Presillion *plus* Stent Systems.
Device success - the attainment of <50% final residual stenosis of the target lesion using any percutaneous method.
Procedural success - Attainment of <50% residual stenosis of the target lesion and no in-hospital death, MI or TLR.
Definite Thrombosis (ARC)- is considered either angiographic confirmed or pathologic confirmed.
Probable Thrombosis (ARC) - is considered to have occurred in the following cases: 1. Any unexplained death within the first 30 days. 2. Irrespective of the time after the index procedure any myocardial infarction (MI) in the absence of any obvious cause which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis

A.8 Observed Adverse Events

Observed adverse event experience with the Presillion stent is derived from the PIONIR study. Major clinical events for this study are shown in Table 10 below. An independent Clinical Events Committee (CEC) adjudicated all clinical endpoint events in this study.

Table 10: In and Out of Hospital Complications Through 360 days

% (Number/Denominator) (95% Confidence Interval)

SAFETY MEASURES	IN HOSPITAL COMPLICATIONS	COMBINED IN AND OUT OF HOSPITAL COMPLICATIONS TO 30 DAYS	COMBINED IN AND OUT OF HOSPITAL COMPLICATIONS TO 180 DAYS	COMBINED IN AND OUT OF HOSPITAL COMPLICATIONS TO 270 DAYS	COMBINED IN AND OUT OF HOSPITAL COMPLICATIONS TO 360 DAYS
TVF (Cardiac death, Target Vessel MI, Clinical driven TVR)	2.2% (6/278) [0.8%, 4.6%]	2.5% (7/277) [1.0%, 5.1%]	4.7% (13/277) [2.5%, 7.9%]	8.7% (24/276) [5.7%, 12.7%]	10.3 (28/273) [6.9%, 14.5%]
• Cardiac Death	0.4% (1/278) [0.0%, 2.0%]	0.4% (1/277) [0.0%, 2.0%]	0.7% (2/277) [0.1%, 2.6%]	1.1% (3/276) [0.2%, 3.1%]	1.1% (3/273) [0.2%, 3.2%]
• Target Vessel MI	2.2% (6/278) [0.8%, 4.6%]	2.5% (7/277) [1.0%, 5.1%]	2.9% (8/277) [1.3%, 5.6%]	3.3% (9/276) [1.5%, 6.1%]	3.3% (9/273) [1.5%, 6.2%]
o Q Wave MI	0.7% (2/278) [0.1%, 2.6%]	0.7% (2/277) [0.1%, 2.6%]	0.7% (2/277) [0.1%, 2.6%]	0.7% (2/276) [0.1%, 2.6%]	0.7% (2/273) [0.1%, 2.6%
o Non-Q Wave MI	1.4% (4/278) [0.4%, 3.6%]	1.8% (5/277) [0.6%, 4.2%]	2.2% (6/277) [0.8%, 4.7%]	2.5% (7/276) [1.0%, 5.2%]	2.6% (7/273) [1.0%, 5.2%]
• Clinically Driven TVR	0.7% (2/278) [0.1%, 2.6%]	1.1% (3/277) [0.2%, 3.1%]	2.9% (8/277) [1.3%, 5.6%]	6.5% (18/276) [3.9%, 10.1%]	8.1% (22/273) [5.1%, 11.9%]
All Death	0.4% (1/278) [0.0%, 2.0%]	0.4% (1/277) [0.0%, 2.0%]	1.1% (3/277) [0.2%, 3.1%]	1.4% (4/276) [0.4%, 3.7%]	1.5% (4/273) [0.4%, 3.7%]
Clinically Driven TLR	0.7% (2/278) [0.1%, 2.6%]	1.1% (3/277) [0.2%, 3.1%]	2.5% (7/277) [1.0%, 5.1%]	5.1% (14/276) [2.8%, 8.4%]	6.2% (17/273) [3.7%, 9.8%]
Stent Thrombosis	0.7% (2/278) [0.1%, 2.6%]	1.1% (3/277) [0.2%, 3.1%]	1.1% (3/277) [0.2%, 3.1%]	1.1% (3/276) [0.2%, 3.1%]	1.1% (3/273) [0.2%, 3.2%]
Bleeding complications	0.0% (0/278) [0.0%, 1.3%]	0.7% (2/277) [0.1%, 2.6%]	0.7% (2/277) [0.1%, 2.6%]	1.1% (3/276) [0.2%, 3.1%]	1.1% (3/273) [0.2%, 3.2%]
Vascular complications	1.4% (4/278) [0.4%, 3.6%]	1.8% (5/277) [0.6%, 4.2%]	1.8% (5/277) [0.6%, 4.2%]	1.8% (5/276) [0.6%, 4.2%]	1.8% (5/273) [0.6%, 4.2%]

B. The BLAST Study

B.1 Study Design

The BLAST study is a Phase II dose-finding, randomized, multi-center, prospective, double blind clinical study (# LA-II-01).

This study compared the results of PCI with implantation of a bare metal stent (Presillion™ stent) in conjunction with use of Liposomal Alendronate, a drug which was administered in a single intravenous dose, to bare metal stenting alone in the treatment of de novo stenotic lesions in native coronary arteries. The data from the control arm (bare metal stenting alone) are considered relevant to this application and are reported below.

The primary efficacy endpoint of this study was the 6-month in-stent late lumen loss, as measured by QCA.

An independent Clinical Events Committee adjudicated all serious adverse event and endpoint adverse events.

Table 11: Summary of the BLAST Study

Study Type	• Multi-center study (n=11), performed in Israel • Phase 2 – dose finding • Double blind • Randomized, 3 arms on 1:1:1 basis: o High LA dose 0.01 mg o Low LA dose 0.001 mg o Placebo IV saline infusion • Prospective • All patients were treated with the Presillion™ *plus* CoCr Coronary Stent on RX System.
Number of patients	• Total: 226 • Placebo group: 57
Lesion criteria	Up to 2 de novo stenotic lesions in native coronary arteries (length ≤ 30 mm) with a reference vessel diameter of 2.50 mm to 3.50 mm
Anti-platelet therapy	• Aspirin indefinitely • Clopidogrel for a minimum of 1 month
Follow up	• Clinical follow up at 30 days • Clinical and angiographic (stent) follow up at baseline and 6 months, including Quantitative Coronary Angiography (QCA). • IVUS at baseline ant 6 months for pre-specified patients. • Yearly contact through 1-5 years
Sponsor	BIOrest Ltd

B.2 Clinical Inclusion/Exclusion Criteria

Only inclusion/exclusion criteria relevant to use of the control device are provided below. Other criteria related to gastrointestinal disease, immunodeficiency, and bone diseases were included in the protocol because of the drug used in the treatment arm and are not listed here.

General Inclusion Criteria

1. Subject is ≥ 18 and ≤ 80 years old.
2. Subject is eligible for percutaneous coronary intervention (PCI).
3. Subject understands the nature of the procedure and provides written informed consent prior to the catheterization procedure.
4. Subject is willing to comply with specified follow-up evaluation and can be contacted by telephone.
5. Subject is an acceptable candidate for coronary artery bypass graft (CABG) surgery.
6. Subject has stable angina pectoris (Canadian Cardiovascular Society (CCS) 1, 2, 3 or 4) or unstable angina pectoris (Braunwald Class 1-3, B-C) or a positive functional

ischemia study (e.g., ETT. SPECT, Stress echocardiography) or a positive noninvasive imaging study (Cardiac CT).

7. Subject is male or a non-pregnant female (Note: females of child bearing potential must have a negative pregnancy test prior to enrollment in the study).

Angiographic Inclusion Criteria

1. Subject is a candidate for elective stenting of up to 2 lesions.
2. Each reference vessel diameter is ≥ 2.5mm and ≤ 3.5mm in diameter by visual estimate.
3. Each target lesion(s) is ≤ 30mm in length by visual estimate (the intention should be to cover the whole lesion with one stent of adequate length).
4. Each target lesion(s) stenosis is ≥ 50% and < 100% by visual estimate.
5. In subjects where two lesions are to be treated in the same vessel, the lesions should be separated by at least 10mm.

General Exclusion Criteria

1. Subject is currently enrolled in another investigational device or drug trial that has not completed the primary endpoint or that clinically interferes with the current study endpoints.
2. Any planned elective surgery or percutaneous intervention within 6 months post-procedure.
3. A previous coronary interventional procedure of any kind within 30 days prior to the procedure.
4. Subject requires a staged procedure of either the target or any nontarget vessel within 9 months post-procedure.
5. Any drug eluting stent (DES) deployment within the past 12 months.
6. Any planned DES deployment during the procedure associated with this study or within 3 months following the index procedure.
7. Co-morbid condition(s) that could limit the subject's ability to participate in the trial or to comply with follow-up requirements, or impact the scientific integrity of the trial.
8. Known hypersensitivity or contraindication to aspirin or clopidogrel or a sensitivity to contrast media, which cannot be adequately pre-medicated
9. Concurrent medical condition with a life expectancy of less than 12 months.
10. Documented left ventricular ejection fraction (LVEF) < 25% at the most recent evaluation.
11. Evidence of ST elevated myocardial infarction (STEMI) or non- STEMI with troponin (cTn) levels greater than or equal to 3 times the normal limit at any time within 72 hours of the intended trial procedure.
12. History of cerebrovascular accident or transient ischemic attack in the last 6 months.
13. Leukopenia (leukocytes $<3.5 \times 10^9$ / liter).
14. Neutropenia (Absolute Neutrophil Count < $1000/mm^3$)
15. Thrombocytopenia (platelets < $100,000/mm^3$)
16. Serum creatinine level >2.5 mg/dl within 7 days prior to index procedure.
17. History of bleeding diathesis or coagulopathy or inability to accept blood transfusions.

18. Known hypersensitivity or contraindication to aspirin, heparin or bivalirudin, clopidogrel and ticlopidine, cobalt, nickel, L-605 Cobalt chromium alloy, Alendronate or sensitivity to contrast media, which cannot be adequately pre-medicated.

Angiographic Exclusion Criteria

1. Unprotected left main coronary artery disease (obstruction greater than 50% in the left main coronary artery that is not protected by at least one non-obstructed bypass graft to the LAD or Circumflex artery or a branch thereof).
2. Any previous stent placement within 15 mm (proximal or distal) of the target lesion(s).
3. Target vessel exhibiting lesions with greater than 60% diameter stenosis outside of a range of 5 mm proximal and distal to the target lesion(s) based on visual estimate or on-line QCA.
4. Target lesion(s) exhibiting an intraluminal thrombus (occupying >50% of the true lumen diameter) at any time.
5. Lesion location that is aorto-ostial or within 5 mm of the origin of the left anterior descending (LAD) or left circumflex (LCX).
6. The target lesion(s) requires treatment with a device other than PTCA prior to stent placement (such as, but not limited to, directional coronary atherectomy, excimer laser, rotational atherectomy, etc.).
7. Target lesion(s) with side branches > 2.0mm in diameter.
8. Target lesion(s) involving a bifurcation (either stenosis of both main vessel and major branch or stenosis of just major branch).
9. Target lesion(s) with severe calcification.
10. Target vessel exhibiting excessive tortuosity that may impede stent delivery and deployment at target lesion(s).
11. Target lesion(s) located in a native vessel distal to an anastomosis with a saphenous vein graft or a left/right internal mammary artery (LIMA/RIMA) bypass.

B.3 Follow-up Schedule

All subjects are followed up to 5 years. All subjects are required to have a hospital or office follow-up visit at 30 days and 6 months, and telephone contact at 1, 2, 3, 4 and 5 years.

B.4 Endpoints

The primary efficacy endpoint is the mean value of in-stent late loss, which is defined as the difference between the post-procedure in-stent minimal lumen diameter (MLD) and the 6 month follow-up angiography in-stent MLD as measured by quantitative coronary angiography (QCA).

Secondary Endpoints Relevant to the Control Arm

Clinical Outcomes

1. Major Adverse Cardiac Events (MACE): defined as death, myocardial infarction (MI - STEMI and NSTEMI), emergent bypass surgery, or clinically driven target lesion(s)

revascularization (TLR) (repeat PCI or CABG) at 30, 180 and 360 days as well as yearly through 5 years post-procedure

2. Clinically driven target lesion(s) revascularization (TLR): defined as reintervention (PCI or CABG) due to stenosis of ≥50% by QCA with ischemic signs and/or symptoms at 30, 180 and 360 days as well as yearly through 5 years post-procedure
3. Target vessel failure (TVF): defined as the composite of cardiac death, target vessel MI (Q or Non Q-Wave), or clinically driven target vessel revascularization (TVR) at 30, 180 and 360 days as well as yearly through 5 years post-procedure
4. Target lesion(s) failure (TLF): defined as the composite of cardiac death, target vessel MI (STEMI and NSTEMI), or clinically driven TLR at 30, 180 and 360 days as well as yearly through 5 years post-procedure
5. All Death at 30, 180 and 360 days as well as yearly through 5 years post-procedure
6. MI (STEMI and NSTEMI) at 30, 180 and 360 days as well as yearly through 5 years post-procedure
7. Composite endpoint of cardiac death or MI at 30, 180 and 360 days as well as yearly through 5 years post-procedure
8. Bleeding or Vascular Complications at 30 days
9. Late Stent Thrombosis at 180 and 360 days as well as yearly through 5 years postprocedure

Based on Clinical and Angiographic Follow-up:

1. Procedure Success: Attainment of < 50% final residual stenosis of the target lesion(s) using any percutaneous method, i.e., the assigned treatment followed by another device (such as an additional or different stent) without the occurrence of MACE prior to hospital discharge

Based on Angiographic Follow-up at 6 months:

1. In-segment percent diameter stenosis (%DS) (within the 5 mm margins proximal and distal to stent)
2. In-stent percent diameter stenosis (%DS)
3. In-segment late loss

4. Binary restenosis (stenosis of >50% of the vessel diameter)
5. In-stent minimum lumen diameter (MLD)
6. In-stent late loss comparison (analyzed on a per-lesion basis)

Based on IVUS Follow-up at 6 months:

1. In-stent percent volume obstruction (%VO)
2. Neointimal hyperplasia (NIH) volume
3. Incomplete stent apposition

B.5 Accountability of PMA Cohort

A total of 74 subjects were enrolled in the placebo arm group of the BLAST study. The primary efficacy analysis set for this trial was the per protocol (PP) analysis set. This population was defined as all randomized patients who signed the written informed

consent, received the correct randomized treatment, had qualified follow-up QCA films, and excluded those patients who withdrew consent or those who had troponin elevations over 10xULN at baseline. The ITT placebo population of 74 yielded a PP placebo population of 57 patients.

At the time of database lock for the 6 month primary endpoint, of 74 ITT subjects enrolled, 90.5% (67) subjects were available for clinical follow-up data analysis. Fifty seven (57) subjects 100% of the PP population had 6 months QCA.

B.6 Study Population Demographics and Baseline Parameters

Table 12 below includes baseline demographics and patient characteristics for the contorl arm of the BLAST trial.

Table 12: Patient Characteristics

	% OF NUMBER OF PATIENTS (57)
Age (years)	58.1±8.2
Male	87.7%
Current smokers	42.6%
Hypercholesterolemia	75.4%
Hypertension	66.7%
Previous MI	30.4%
Diabetes • Diet controlled • Oral Hypoglycemics • Insulin	38.6% 22.7% 68.2% 9.1%

B.7. Safety and Effectiveness Results

Principal effectiveness and safety results are shown in Table 13.

At 6 months follow-up, the mean (±SD) of in-stent late lumen loss for the 57 per-protocol (PP) placebo arm patients was 0.86mm (± 0.60 mm).

The overall MACE rate at 180 days for the placebo group was 25.0% (14/56) with 19.65% (11/56) MIs (all being target vessel non ST elevation MIs) and 7.1% (4/56) clinically driven TLR events. (Note that a patient may have experienced more than one such event.) There were no deaths or emergent CABG events reported through 180 days.

The overall rate of TLF and TVF at 180 days was 25.0% (14/56). There was only one (1.8%) late stent thrombosis event through 180 days of follow-up in the placebo group.

The rate of peri-procedural TV-MI in the BLAST study was 17.5% compared to a rate of 2.2% in the PIONIR study. The difference in these rates is largely attributable to differences in definitions utilized in the two studies. The PIONIR study used the

historical WHO definition based on total CK, whereas the BLAST study used the ARC definition utilizing levels of troponin, a more sensitive biomarker. When the events in the PIONIR study are adjudicated against the ARC definition, the resulting rate is 12.6%. Additionally, when patient and lesion characteristics are considered, the BLAST patient study enrolled a more complex patient population compared to the PIONIR study, with higher rates of unstable angina and diabetes and more complex lesion characteristics. Given these differences between studies, the difference in MI rates between studies did not raise a safety concern.

The principal safety and effectiveness results are shown in Table 13 below, which continues on the subsequent pages. The Quantitative Angiographic Analysis and clinical outcomes are generally consistent with the outcomes of the PIONIR study.

Table 13: Principal Safety and Effectiveness Results

Effectiveness Measures	**Placebo (N=57 Patients)**	**[95% CI]**
Acute Success		
Lesion Success	100.0% (65/65)	[94.5%,100.0%]
Procedure Success	82.5% (47/57)	[70.1%,91.3%]
Treatment Success	82.5% (47/57)	[70.1%,91.3%]
Post Procedure		
In-Stent Minimal Lumen Diameter (MLD, in mm)		
Mean±SD (N)	2.63±0.48 (57)	[2.50,2.75]
Range (min,max)	(1.84,3.65)	
Median	2.62	
In-Stent Percent Diameter Stenosis (% DS)		
Mean±SD (N)	6.23±5.94 (57)	[4.66,7.81]
Range (min,max)	(-6.98,23.33)	
Median	5.99	
In-Segment Minimal Lumen Diameter (MLD, in mm)		
Mean±SD (N)	2.36±0.43 (57)	[2.25,2.47]
Range (min,max)	(1.53,3.25)	
Median	2.29	
In-Segment Percent Diameter Stenosis (% DS)		
Mean±SD (N)	15.66±6.56 (57)	[13.92,17.40]
Range (min,max)	(0.23,26.81)	
Median	15.77	
Follow-up (6-month)		
Follow-up In-Stent Minimal Lumen Diameter (MLD, in mm)		
Mean±SD (N)	1.77±0.80 (57)	[1.55,1.98]
Range (min,max)	(0.00,3.41)	
Median	1.81	
Follow-up In-Stent Percent Diameter Stenosis (% DS)		

Effectiveness Measures	Placebo (N=57 Patients)	[95% CI]
Mean±SD (N)	36.64±24.88 (57)	[30.04,43.24]
Range (min,max)	(-6.40,100.00)	
Median	35.40	
Follow-up In-Segment Minimal Lumen Diameter (MLD, in mm)		
Mean±SD (N)	1.68±0.72 (57)	[1.49,1.87]
Range (min,max)	(0.00,3.00)	
Median	1.61	
Follow-up In-Segment Percent Diameter Stenosis (% DS)		
Mean±SD (N)	39.84±21.68 (57)	[34.08,45.59]
Range (min,max)	(3.81,100.00)	
Median	35.58	
Late Loss In-Stent (mm)		
Mean±SD (N)	0.86±0.60 (57)	[0.70,1.02]
Range (min,max)	(-0.08,2.24)	
Median	0.83	
Late Loss In-Segment (mm)		
Mean±SD (N)	0.68±0.58 (57)	[0.53,0.84]
Range (min,max)	(-0.37,1.81)	
Median	0.62	
In-Stent Binary Restenosis	26.3% (15/57)	[15.5%,39.7%]
In-Segment Binary Restenosis	26.3% (15/57)	[15.5%,39.7%]
Safety Measures – Principal Adverse Events through 180 days		
In-Hospital MACE	17.5% (10/57)	[8.7%,29.9%]
Out-of-Hospital MACE to 180 Days	7.1% (4/56)	[2.0%,17.3%]
MACE to 180 days	25.0% (14/56)	[14.4%,38.4%]
Type I MI (STEMI, NSTEMI)*	19.6% (11/56)	[10.2%,32.4%]
Type II MI (Q-Wave, Non-Q-Wave)*	19.6% (11/56)	[10.2%,32.4%]
Cardiac Death or MI	19.6% (11/56)	[10.2%,32.4%]
Clinically-Driven Target Lesion Revascularization (TLR)	7.1% (4/56)	[2.0%,17.3%]
Target Vessel Failure (TVF)	25.0% (14/56)	[14.4%,38.4%]
Target Lesion Failure (TLF)	25.0% (14/56)	[14.4%,38.4%]
Bleeding Complications	0.0% (0/56)	[0.0%,6.4%]
Vascular Complications	0.0% (0/56)	[0.0%,6.4%]
Stent Thrombosis	1.8% (1/56)	[0.0%,9.6%]

* Each MI was categorized for both groups.

C. The Belgian Registry

C1. Study Design

The Belgian Registry is a non-randomized, multi-center, single-arm registry that was initiated as a 30-day follow up after the procedure. At a later stage, the follow-up period was prolonged to include an additional data point (as close as possible to, but after, the 6-month post-procedure date).

The main objective of this study is to evaluate the safety of Presillion™ *plus* CoCr Coronary Stent on RX System in the treatment of de novo stenotic lesions in native coronary arteries.

The primary safety measure is a composite of MACE (includes cardiac death, MI [Q-wave and Non-Q-wave] and clinically driven Target Lesion Revascularization [TLR]) at 30 days and 6 months post procedure.

Table 14: Summary of the Belgian Registry

FACTOR	DETAILS
Study Type	• Multi center (n=8), performed in 7 centers in Belgium and 1 center in Luxemburg • Single arm • Direct stenting (stent implantation without balloon pre-dilatation) was allowed to most closely address daily routine clinical practice.
Number of patients	101 patients enrolled for the study • 30-day follow up: 101 • 6-month to 1 year follow up: 89
Lesion criteria	Up to two (2) de novo native coronary artery lesions with a maximum lesion length of 30mm in a maximum of two major coronary arteries with reference vessel diameter ≥ 2.5mm and ≤ 4.0mm by visual estimation.
Anti-platelet therapy	• Aspirin, indefinitely • Clopidogrel, for a minimum of 1 month
Follow up	• 30 days • Prolonged to 6 months, up to 1 year.
Sponsor	Cordis, a J&J company

C2. Clinical Inclusion/Exclusion Criteria

General Inclusion Criteria

1. The patient must be ≥18 years of age.
2. Patient is eligible for percutaneous coronary intervention (PCI).
3. Acceptable candidate for coronary artery bypass surgery (CABG).
4. Female patients of childbearing potential must have a negative pregnancy test within 7 days prior to enrolment and utilize reliable birth control for trial duration.
5. Diagnosis of angina pectoris as defined by Canadian Cardiovascular Society Classification (CCS I, II, III, IV) or unstable angina pectoris (Braunwald Classification B&C, I-II-III) or patients with documented silent ischemia.
6. Treatment of up to two de novo native coronary artery lesions in a maximum of two major coronary arteries.
7. Target reference vessel diameter of both lesions must be ≥2.5mm and ≤4.0mm in diameter (visual estimate).
8. Target lesion length must be ≤30mm and be covered by one study stent.
9. Target lesion stenosis for both lesions is > 50% and <100% (visual estimate).
10. At least TIMI I coronary flow.
11. Patient is willing to comply with the specified followup evaluation.
12. Patient must provide written informed consent prior to the procedure using a form that is approved by the local Ethics Committee.

General Exclusion Criteria

1. Recent myocardial infarction (either STEMI or non STEMI < 48 hours prior to planned index procedure).
2. The patient has unstable angina classified as Braunwald A I-II-III.
3. The patient has unprotected left main coronary artery disease (stenosis >50%).
4. A significant (> 50%) stenosis proximal or distal to the target lesion.
5. Angiographic evidence of thrombus within the target lesion.
6. Heavily calcified lesion and/or calcified lesion, which cannot be successfully predilated and/or an excessively tortuous vessel which makes it unsuitable for stent delivery and deployment.
7. Left ventricular ejection fraction ≤ 25%.
8. Totally occluded lesion (TIMI 0 level).
9. The patient has impaired renal function (creatinine3.0mg/dL) at the time of treatment.
10. The patient had a Cerebrovascular Accident (CVA) within the past 6 months.
11. Prior stent within 10mm of target lesion.
12. The target lesion is ostial in location (within 3.0mm of vessel origin).
13. The target lesion involves a bifurcation with a diseased (>50% stenotic) branch vessel ≥ 2.0mm in diameter (or side branch requiring intervention of protection).
14. The target lesion is located in a bypass graft. *Note: stenting of lesions in bypassed native coronary arteries is allowed.*
15. Known allergies to the following: aspirin, clopidogrel bisulfate (Plavix ®) and ticlopidine (Ticlid ®), heparin, cobalt chromium, contrast agent (that cannot be managed medically).
16. The patient has any significant medical condition which in the investigator's opinion may interfere with the patient's optimal participation in the study.

17. The patient is currently participating in an investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the study endpoints.
18. Intervention of another lesion within 30 days prior to, or is planned or highly probably to be performed 30 days after the index procedure.

C3. Follow-up Schedule

All subjects are followed up to 1 year. All subjects are required to have a hospital or office follow-up visit at 30 days, 6 months, and 1 year.

C4. Clinical Endpoints

The primary endpoint was MACE defined as cardiac death, myocardial infarction, or target lesion revascularization.

Secondary Endpoints

1. In-hospital MACE
2. Clinically-driven Target Lesion Revascularization
3. Clinically-driven Target Vessel Revascularization
4. Target Vessel Failure
5. Myocardial infarction
6. Major bleeding
7. Stroke
8. Procedural success
9. Lesion success
10. Device success

C5. Accountability of PMA Cohort

At the time of database lock, of 101 subjects enrolled, 88.1% (89) subjects were available for analysis at the 12 month study completion. Clinical information were not obtained for 12 subjects (11.9%) due to death , pending or withdrawn informed consent.

Table 15: Patient Accountability

Total subjects enrolled	101
Total subjects completed 1 year follow-up	89 (88.1%)
Total subjects with no clinical information at 1 year	12 (11.9%)
Cardiac death	1 (1.1%)
Pending or withdrew consent	11 (10.89%)

C5. Study Population Demographics and Baseline Parameters

Table 16 below includes the baseline demographics and patient characteristics for the Belgian registry.

Table 16: Patient Characteristics

CHARACTERISTIC	% OF NUMBER OF PATIENTS (101)
Age, mean (years)	66.1±10.6
Male	69.3%
History of smoking	64.4%
Hypercholesterolemia	76.2%
Previous MI	24.8%
Diabetes	1.0%

C6. Safety and Effectiveness Results

Principal effectiveness and safety results are shown in Tables 17 and 18. The information gathered in this registry indicates that the safety profile of the Presillion stent in the treatment of de novo coronary artery stenosis is generally consistent with the results of the PIONIR study.

Table 17: Principal safety and effectiveness results through 1 month (N=101)

	(%)
Primary endpoint:	
MACE (cardiac death, myocardial infarction, target lesion revascularization)	0
Secondary endpoints:	
In-hospital MACE	0
Clinically-driven Target Lesion Revascularization	0
Clinically-driven Target Vessel Revascularization	0.99
Target Vessel Failure	0
Myocardial infarction	0
Major bleeding	0
Stroke	0
Procedural success (n=101)	99.0
Lesion success (n=111)	100
Device success (n=111)	97.3

Table 18: Principal safety and effectiveness results through 180 Days or Beyond

	(%)
Cardiac death	1.1
Non-cardiac death	0
Non-fatal QMI	0
CABG	0
Ischemia driven TVR	4.5
Ischemia driven non TVR	1.1
Stroke	1.1
Stent thrombosis	1.1
TVF (cardiac death, MI, TVR)	5.6
MACCE (death, stroke, MI, CABG, TVR, non TVR)	7.9

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Cardiovascular disease is the leading cause of death for both women and men in the U.S. and coronary artery disease is a major cause of morbidity and mortality in women. It is estimated that the prevalence of coronary artery disease in the United States is 9.1% (9,200,000) in males and 7.0% (8,400,000) in females for adults at least 20 years old according to the American Heart Association 2010 Update.[1] However, it is estimated that only 36% of annual PCIs are performed in women.[2] In PCI clinical trials, women represent only 25-35% of the enrolled populations, and there are relatively little gender-specific data. The disproportionate enrollment distribution in these trials may be partly attributable to gender differences in symptoms and pathophysiology[3] which may lead to under-diagnosis and under-referral of female patients with CAD. Women tend to have worse clinical outcomes compared to men, most likely due to their higher baseline risk profile and more complex angiographic characteristics. [4, 5, 6]

Gender-based analysis of the PIONIR study

A post hoc evaluation of the PIONIR clinical study was conducted to identify possible sex-based differences in baseline characteristics and clinical outcomes. The PIONIR study was not designed nor powered to study safety and effectiveness differences between sexes, so this analysis is considered exploratory without definitive conclusions.

In the PIONIR study, 66/278 (23.7%) subjects were female and 212/278 (76.3%) were male. In comparison, the prevalence of coronary artery disease (CAD) is estimated at 9.2 million in males

and 8.4 million in females for adults age 20 and older in the United States (i.e., the CAD population is estimated to be 52.2% males and 47.7% females).

The disproportionate enrollment distribution in the PIONIR study may be partly attributable to the fact that women have always been underrepresented in clinical trials of coronary interventions. In studies of PCI published between 1990 and 2005, women represented only 15% to 38% (mean = 29.0% women, n = 86,137) of the patient population.[6]
Women are also underrepresented in contemporary studies of coronary stenting. A review of the literature identified only 7 studies with sex-stratified data, with the inclusion of women ranging from 20% to 28% (mean = 25.1% women; n= 2,954).[7, 8, 9, 10, 11, 12, 13]

With the inclusion of 23.7% women, the PIONIR study of the Presillion™ *plus* Stent System is representative of contemporary studies.

Table 19 and Table 20 display baseline demographics and angiographic characteristics, respectively.

Table 19: Baseline demographics by gender

	Male (N=212)	Female (N=66)	Difference [95% CI]	P-value
Age (years)	64.3±10.2	69.0±11.0	-4.7[-7.6,-1.7]	0.002
Current smokers	24.1%	22.7%	1.3%[-10.3%,13.0%]	<.001
Hypercholesterolemia	75.8%	77.3%	-1.4%[-13.1%,10.2%]	0.870
Hypertension	69.3 %	81.8%	-12.5%[-23.7%,-1.3%]	0.058
Previous MI	28.3%	26.2%	2.1%[-10.1%,14.4%]	0.874
Diabetes	19.8%	22.7%	-2.9%[-14.4%,8.5%]	0.604
Diet controlled	4.7%	1.5%	3.2%[-0.9%,7.3%]	0.468
Oral Hypoglycemics	10.4%	18.2%	-7.8%[-18.0%,2.4%]	0.130
Insulin	4.7%	3.0%	1.7%[-3.3%,6.7%]	0.737

Table 20: Angiographic characteristics by gender

Measure	Male (N=212)	Female (N=66)	Difference [95% CI]	P-value
Vessel Location				0.237
LAD	35.2% (75/213)	38.8% (26/67)	-3.6%[-16.9%,9.7%]	
LCX	29.1% (62/213)	31.3% (21/67)	-2.2%[-14.9%,10.4%]	
RCA	35.7% (76/213)	28.4% (19/67)	7.3%[-5.2%,19.9%]	
LCMA	0.0% (0/213)	1.5% (1/67)	-1.5%[-4.4%,1.4%]	
Length				0.805
1 - 10 mm	54.9% (117/213)	50.7% (34/67)	4.2%[-9.5%,17.9%]	
10 - 20 mm	40.4% (86/213)	43.3% (29/67)	-2.9%[-16.5%,10.7%]	
> 20 mm	4.7% (10/213)	6.0% (4/67)	-1.3%[-7.6%,5.1%]	
Thrombus	0.9% (2/213)	0.0% (0/67)	0.9%[-0.4%,2.2%]	1.000
Calcification				0.003
Mild	82.2% (175/213)	71.6% (48/67)	10.5%[-1.4%,22.5%]	
Moderate	13.6% (29/213)	11.9% (8/67)	1.7%[-7.4%,10.7%]	
Severe	4.2% (9/213)	16.4% (11/67)	-12.2%[-21.5%,-2.9%]	

In the post-hoc analysis conducted on the intention-to-treat population, the only significant sex difference observed was a lower rate of target vessel myocardial infarction in women at the 270-day follow-up (1.9% vs 7.6%, p = 0.038). Although not significant (p = 0.057), the rate of cardiac death at 180-day and 270- day follow-up was higher in women (3.3%) than men (0.0%). Due to the modest sample size of this study, this analysis and any interpretation are limited.

Table 21 below displays safety and effectiveness results by gender.

Table 21: Safety and Effectiveness Results by Gender (PIONIR study)

	MALE (N=212)	FEMALE (N=66)
PRIMARY ENDPOINT		
TVF-Free at 270 Days	92.4%	87.9%
EFFECTIVENESS MEASURES		
Lesion Success	100.0% (214/214)	100.0% (67/67)
Device Success	98.1% (210/214)	98.5% (66/67)
Procedure Success	98.6% (209/212)	95.5% (63/66)
TVF-Free at 30 Days	98.1%	95.5%
Clinically Driven TLR-Free at 30 Days	99.1%	98.5%
Clinically Driven TVR-Free at 30 Days	99.1%	98.5%
Clinically Driven TLR-Free at 270 Days	94.8%	95.4%
Clinically Driven TVR-Free at 270 Days	93.8%	92.3%
SAFETY MEASURES		
TVF to 30 Days	1.9% (4/211)	4.5% (3/66)
All Death to 30 Days	0.0% (0/211)	1.5% (1/66)
Target Vessel MI to 30 Days	1.9% (4/211)	4.5% (3/66)
TVF to 270 Days	7.6% (16/210)	12.1% (8/66)
All Death to 270 Days	1.0% (2/210)	3.0% (2/66)
Target Vessel MI to 270 Days	1.9% (4/210)	7.6% (5/66)
Stent Thrombosis to 270 Days	1.0% (2/210)	1.5% (1/66)
Bleeding Complications at Discharge	0.0% (0/212)	0.0% (0/66)
Vascular Complications at Discharge	1.9% (4/212)	0.0% (0/66)

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Cardiovascular Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

The safety and effectiveness of the Presillion™ *plus* CoCr Coronary Stent on RX System are based on the results obtained from: evaluation of biocompatibility; *in vitro* engineering testing; *in vivo* animal testing; sterilization information; shelf life testing; and clinical studies. These studies revealed the following:

A. Safety Conclusions

The biocompatibility testing and *in vivo* animal testing conducted on the Presillion™ *plus* CoCr Coronary Stent on RX System demonstrate that the acute and chronic *in vivo* performance characteristics of the product provide reasonable assurance of safety and acceptability for clinical use.

The *in vitro* engineering testing conducted on the stent and delivery systems demonstrated that the performance characteristics met the product specifications. The test results obtained from the sterilization testing demonstrated that the product can be adequately sterilized and is acceptable for clinical use. The functional shelf life and package integrity testing demonstrated that the product can be labeled with a shelf life of 2 years.

The results of the PIONIR study demonstrated the safety of the Presillion™/ Presillion™ *plus* CoCr Coronary Stent on RX System through evaluation of the composite endpoint of target vessel failure (TVF – cardiac death, target vessel myocardial infarction (MI [Q wave or non-Q wave]), or clinically driven target vessel revascularization (TVR) by percutaneous or surgical methods) within 270 days of the treatment, similar toother stents approved for the same indications for use.

B. Effectiveness Conclusions

The results of the PIONIR study demonstrated that the primary endpoint of TVF within 270 days of treatment with the Presillion™/ Presillion™ *plus* CoCr Coronary Stent on RX System was 8.7% and the upper bound of the exact one-sided 95% confidence interval was 12.7%. Since this upper bound is less than the established performance goal of 16.46%, the performance goal is considered to have been met.

C. Overall Conclusions

The clinical and preclinical testing conducted demonstrated that the Presillion™ plus CoCr Coronary Stent on RX System provides a reasonable assurance of safety and effectiveness when used as indicated in accordance with the instructions for use.

XIII. CDRH DECISION

CDRH issued an approval order on April 12, 2012. The final conditions of approval cited in the approval order are described below.

1. *The Continued Follow-up of BLAST Placebo Cohort*: The study must be conducted as per agreement reached on January 24, 2012 (September 23, 2009, version 1.0, and updates on January 12, 2012). The prospective, observational, single arm study will consist of continued follow up of the premarket cohort of the placebo patients from the BLAST study who will be followed annually.

The individual endpoints are major adverse cardiac events (MACE), clinically driven target lesion revascularization (TLR), target vessel failure (TVF), target lesion failure (TLF), all cause mortality, myocardial infarction (MI), composite cardiac death/MI, and stent thrombosis.

The study population will consist of the patients in the BLAST placebo cohort treated with Presillion plus CoCr Coronary Stent System per device labeling. Information on clinical outcomes will be collected annually through 5 years post-procedure on at least 80% of patients enrolled (excluding those discontinued due to death) in the BLAST clinical trial.

2. *The Enrollment of a New US Cohort Study:* The study must be conducted as per agreement reached on January 24, 2012 (P110004/A005, protocol version 0.4). The study will consist of a newly enrolled, non-randomized, multi-center, prospective, single arm clinical study of patients treated with the Presillion *plus* CoCr Coronary Stent System for the treatment of *de novo* stenotic lesions in native coronary arteries in the US population.

   The primary effectiveness objective is to demonstrate that the 3-year incidence of TVF (cardiac death, target vessel myocardial infarction, or clinically driven target vessel revascularization) is less than the performance goal of 33% derived from development of a meta-analysis of five bare metal stent trials (standard of care). The expected rate for TVF at 3 years for Presillion *plus* CoCr Coronary Stent System = 22%.

   A secondary objective is to assess long term safety. Secondary endpoints are all-cause mortality, cardiac death, all cause MI, target vessel MI, clinically driven TVR, acute success rates, and stent thrombosis.

   The study population will consist of adult patients with symptomatic ischemic heart disease due to a single *de novo* stenotic lesions contained within native coronary artery with reference vessel diameter between 2.5 mm and 4.0 mm and lesion length $\leq$ 30 mm that is amenable to percutaneous revascularization with percutaneous coronary intervention with stent deployment. Clinical outcomes will be collected through 3 years post-procedure. In order to demonstrate that the Presillion *plus* CoCr Coronary Stent System meets the performance goal of 22% after three years, you must enroll at least 131 patients for 80% power (one sided α=0.05).

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

1. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 2010; 121:e46-215.
2. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009; 119(3):e21-181.
3. Shaw LJ, Bairey Merz CN, Pepine CJ, et al. Insights From the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: Gender Differences in Traditional and Novel Risk Factors, Symptom Evaluation, and Gender-Optimized Diagnostic Strategies. J Am Coll Cardiol 2006 47: S4-20.
4. Mahoney EM, Jurkovitz CT, Chu H, Becker ER, Culler S, Kosinski AS, et al. Cost and cost-effectiveness of an early invasive vs conservative strategy for the treatment of unstable angina and non-ST-segment elevation myocardial infarction. *Jama* 2002; 288(15):1851-8.
5. Akhter N, Milford-Beland S, Roe MT, Piana RN, Kao J, Shroff A. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *Am Heart J* 2009; 157(1):141-8.
6. Vaina S, Voudris V, Morice M-C, de Bruyne B, Colombo A, Macaya C, Richardt, G, Fajadet, J et al. Effect of gender differences on early and mid-term clinical outcome after percutaneous or surgical coronary revascularization in patients with multivessel coronary artery disease: Insights from ARTS I and ARTS II. *EuroInterv*. 2009; 4(4):492-501.
7. Mehilli J, Kastrati A, Bollwein H, et al. Gender and restenosis after coronary artery stenting. Eur Heart J 2003;24:1523-30.
8. Moriel M, Feld, S, Almagor Y, et al. Results of coronary artery stenting in women versus men: A single center experience. Isr Med Assoc J 2003;5:398-402.
9. Lansky AJ, Costa RA, Mooney M, et al. Gender-based outcomes after paclitacxel-eluting stent implantation in patients with coronary artery disease. J Am Coll Cardiol 2005;45:1180-5.
10. Salinas E, Nikolsky E, Lansky AJ, et al. Gender-specific outcomes after sirolimus-eluting stent implantation. J Am Coll Cardiol 2007;50:2111-6.
11. Presbitero P, Belli G, Zavalloni D, et al. ''Gender paradox'' in outcome after percutaneous coronary intervention with paclitaxel-eluting stents. EuroIntervention 2008;4:345-50.
12. Onuma Y, Kukreja N, Daemen J, et al. Impact of sex on 3-year outcome after percutaneous coronary intervention using bare-metal and drug-eluting stents in previously untreated coronary artery disease. J Am Coll Cardiol Intv 2009;2:603-10.

13. Kralev S, Hennig O, Lang S, et al. Sex-based differences in clinical and angiographic outcomes in patients with ST-elevation myocardial infarction treated with concomitant use of glycoprotein IIb/IIIa inhibitors. Cardiol J2010;17:580-6.